

Aus dem Pathologisch-Anatomischen Institut der Universität Basel
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(Arbeit unter der Leitung von Prof. Fred. C. Roulet)

Malignant Nephrosclerosis and Renal Tuberculosis

**Report of a Case with Granulomatous Periarteritis
Nodosa, Tuberculous Nephritis, and Hypertension.**

Inaugural-Dissertation

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Introduction. The combination of Periarteriitis nodosa and Tuberculosis, a very infrequent event, has been reported in some detail by *Boss* in a paper out of the same Institute of Pathology at Basel (53). The central problem of the following paper will be a similar combination, but with the added presence of malignant nephrosclerosis and sarcoid-like granulomas. The histological picture gives one the impression of transition from one type of granuloma to the next; no sharp differentiation being present. One suspects very strongly therefore, that malignant nephrosclerosis, Sarcoid, and P. nodosa can all be due to the toxic tuberculo-proteins released into the bloodstream from tuberculous foci.

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Case report. The patient, a forty-year-old woman, entered the Citizens' Hospital in April, 1951. Her only child was nephrectomized due to renal tuberculosis, her husband having died of renal and pulmonary tuberculosis just before the patient's present illness. At twenty-two, she had a large tuberculous abscess removed by section of the eleventh rib. She remained well until four years before her hospital entrance, when she had a tonsillectomy after recovery from a severe Angina with high fever. She had chronic tonsillitis as a child. At this time there was no evidence of kidney involvement. A period of well-being followed until April, 1950, when she had a marked hemorrhage, probably from a myoma uteri. Her blood pressure was 240 systolic; urine negative for red cells. Occipital headaches were attributed to overwork and worry connected with her husband's death.

In October 1950, stenocardial pains occurred; ECGs showing myocardial damage and left hypertrophy. Albuminuria was present, but IV pyelograms were normal. In December, reduced visual acuity and visual disturbances occurred. Eye-grounds showed retinopathia angiospastica renalis. Her general condition was poor, the diastolic pressure remaining high despite energetic therapeutic measures. She had a diffuse Struma and a + 27 BMR. No bloody stools. Weight loss about eighteen pounds in four months. BP 265/150. A toxic anemia was present.

To recapitulate, the disease began clinically with hypertension one year before entrance into the Hospital, then albuminuria for six months, visual disturbances four months, and exitus letalis inside of one month, during which time the patient was uremic: Hb 62%, RBC 2.6 million, WBC 6,000, SR 34/62 mm., serum cholesterol 279 mg.%, NPN 60 mg.%, BUN 75-146 mg.%, negative Lowenstein cultures.

Exitus attended by signs of cerebral hemorrhage and central respiratory failure.

Autopsy. At necropsy, the left kidney weighed 140 grams, the right one weighing only 60 grams. Stripping of the capsule was a little difficult, revealing a coarsely granular surface studded with small yellow nodules and larger star-shaped connective tissue scars. The surface was spotted grayish yellow and red. Section showed a thin cortex and no sharp boundaries from the brownish red medulla. The kidneys were markedly contracted. The spleen was an early "Fleckmilz" (spotted spleen). The liver weighed 1,640 grams, with some fatty degeneration. The heart was enlarged (480 grams) and showed fatty degeneration. The brain was edematous and the basal vessels sclerotic, with a massive pontine hemorrhage that had broken into the fourth ventricle. The paratracheal and para-aortic lymph nodes were caseous.

Microscopic examination. The lymph nodes were tuberculous, the pancreas affected by changes similar to periarteritis nodosa, marked round cell infiltration, and arteriosclerosis. In the spleen, some necrotic change of arterioles and small arteries was conspicuous besides the arteriolosclerosis. There were arteriolosclerosis and some miliary tubercles in the liver. The heart muscle was hypertrophic.

The kidneys showed chiefly two sets of changes: 1. the typical picture of a malignant nephrosclerosis, and 2. irregularly occurring, extensively distributed granulomatous processes in the renal cortex. Analysis of these two groups

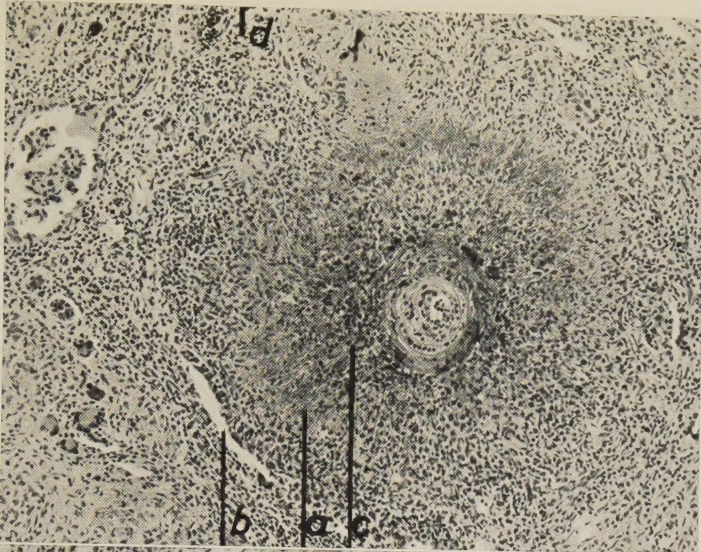


Fig. 1.

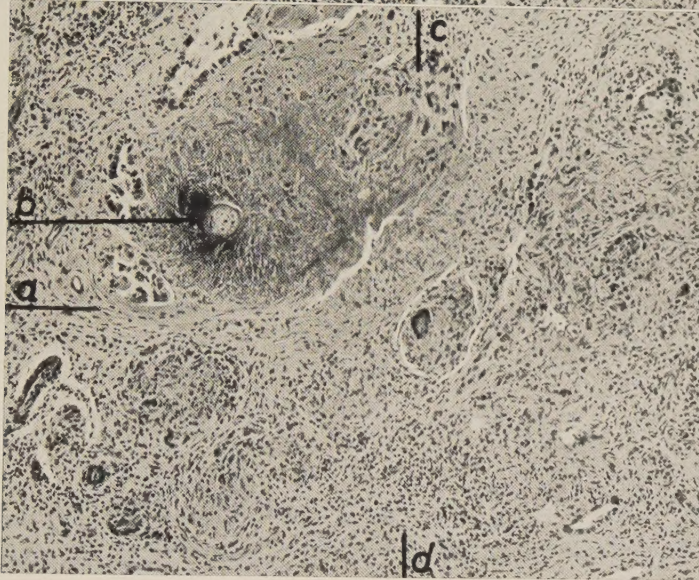


Fig. 2.

Fig. 1. (a) Large perivascular granuloma, (b) with concentrically arranged palisade-like epithelioid cells, (c) central necrosis, and the vessel lumen almost entirely occluded by marked intimal overgrowth; the media is infiltrated with round cells, (d) giant cell. 125 $\times$. H. and E.

Fig. 2. (a) Showing the connective tissue overgrowth in the interstitium, (b) surrounding a well-developed perivascular granuloma with a necrotic area. Centrally, an arteriole with necrosis of all its layers, (c) the remains of a glomerulus with early granuloma formation, (d) infiltration by round cells. 100 $\times$. H. and E.

of changes shows that the arteriolonecroses, often extra-ordinarily widespread, are spottily distributed along the course of the arterioles, and consist of a fibrinoid necrosis of the walls with severe narrowing of the lumina, while necrotic leucocytes, and/or growth of connective tissue is evident periarterially. Often, a muff-like granuloma with its cells arranged in a palisade form surround the arterioles. The cells are mostly histiocytic, some with oval nuclei, their cytoplasm pointing toward the central necrosis. Between them are round cells and lymphocytes, with a few plasma cells (Fig. 1).

The centrally located, eosin stained fibrinoid necroses in these granulomas have a bright red color. The changes described above also appear in medium-sized arteries, then showing the picture of a panarteriitis with predomination of the periarteriitic processes (Fig. 1), by which a large concentrically arranged granuloma is formed, sometimes with the necroses spottily arranged. Where longer stretches of vessels are involved, hemorrhages have occurred. The changes typical of malignant nephrosclerosis can be seen in the glomeruli: i.e., spotty fibrinoid necroses that reach from the vasa afferentia to the glomerular capillary loops, circumscribed stases, exudation into the capsular spaces, synechia, total necroses, and transformation of glomeruli into hyaline scars (Fig. 2).

The second set of changes consists of a collection of larger granulomatous foci, spotty in occurrence, commonest where the vascular damage described above is most intensive, sometimes forming a collar around the largest arteriitic foci (Figs. 2, 3, 4). They are formed from epithelioid cells with finely granular cytoplasm and pale oval nuclei, often arranged radially around a small central necrosis, in which giant cells have formed. The giant cells are of various sizes (56-140 μ), with oval, chromatin-rich nuclei. These cells correspond closely to the Langhans giant cell. With many of these granulomas, one receives the impression they are tubercles. Bacilli could be demonstrated nowhere, and it is further noteworthy that giant cells occur sometimes alone or with very few epithelioid cells, and in regions where the stroma between the tubuli had increased significantly in amount and was infiltrated with round cells. Further significant is the fact that upon closer study, the shadows of necrotic arterioles can be made out in the centers of these noduli (Fig. 4). Several stages can be traced, until gradually no vessels are visible. Rarely, these granulomas occur at the vascular pole of a glomerulus, always with considerable lymphocytic infiltration (Fig. 2, 5).

Here and there, the granulomas lie between the tubuli, which are widened, filled with casts, and in places show fatty and hyaline droplet degeneration of the tubular epithelium. Further, the tubular apparatus also shows irregular growths in many places, with bending of the tubule and epithelial proliferation, sometimes crescent-shaped, surrounding small granulomas like a cap, strongly resembling glomeruli, making them very difficult to differentiate.

In the medulla, there are no granulomas of any size. In the stroma, there are diffuse, loosely packed round cell aggregates. A good deal of the tubuli are widened and filled with casts.

One can conclude that the granulomatous changes are rather closely bound to the arteriolonecrotic processes, as if they were an organization phase of the acute necrotizing process.

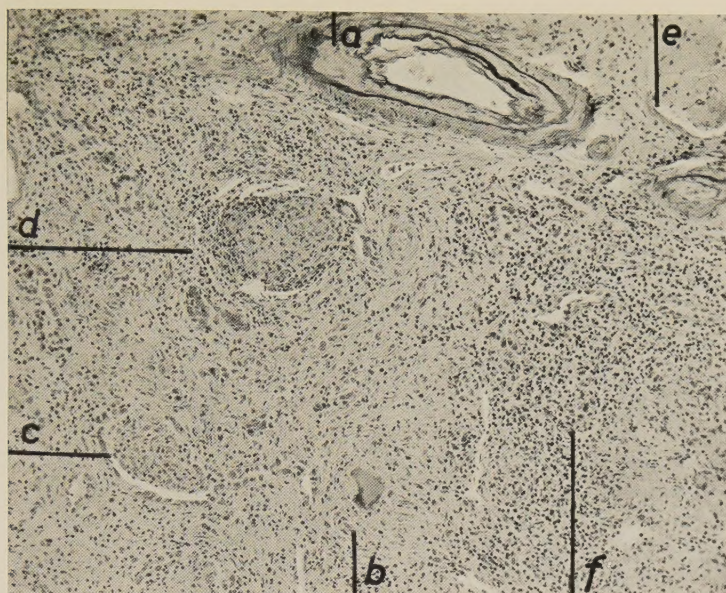


Fig. 3.

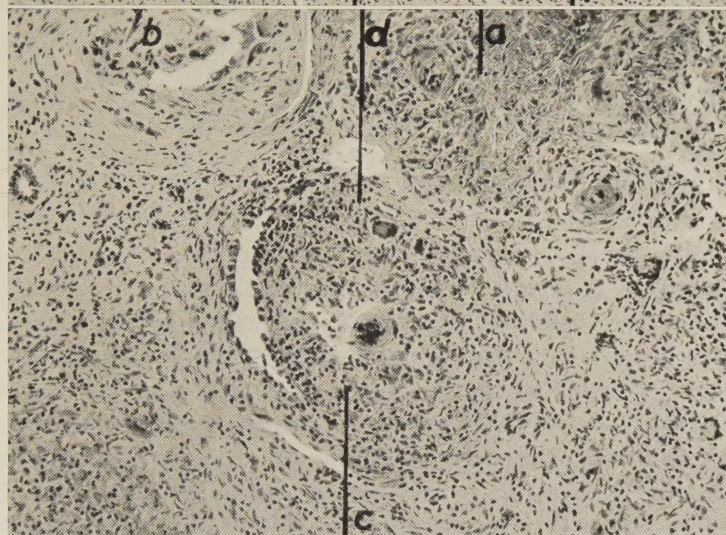


Fig. 4.

Fig. 3. (a) A larger artery showing elastica lamellation and reduced lumen, (b) a granuloma with a giant cell, (c) a glomerulus in the process of breakdown, with its clearly visible urinary pole, (d) another stage in the breakdown process, with the lumen of the vas afferens obliterated, (e) a hyalinized glomerulus (the last stage), (f) round cell infiltration. 100 $\times$. H. and E.

Fig. 4. (a) A large necrotic area between two dysplastic arterioles, (b) the remains of a glomerulus, (c) granuloma showing central arteriolonecrosis, the vascular lumen thrombosed, (d) and finally, a small giant cell. 125 $\times$. H. and E.

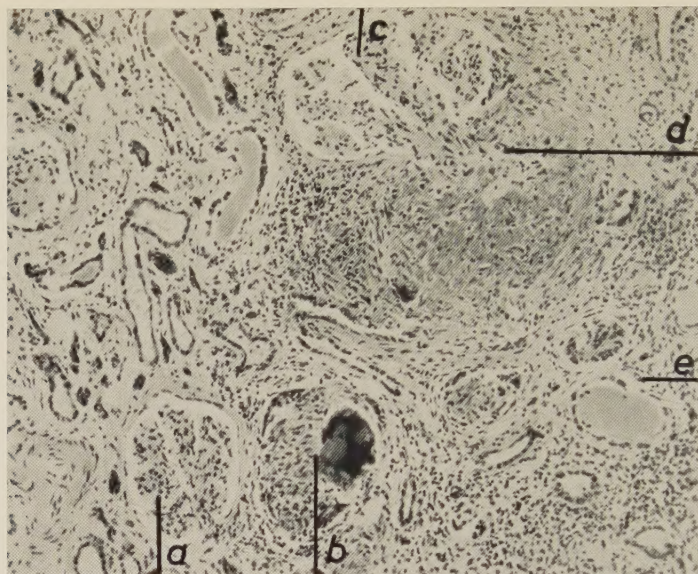


Fig. 5. (a) Fairly well-preserved glomerulus, with thickened Bowman's capsule, (b) neighboring glomerulus in the process of breakdown, with giant cell, (c) large glomerulus showing synechiae, collapsed capillary loops, and (d) a marked concentric necrosis beneath its vascular pole. The vas afferens is occluded, (e) enlarged tubuli filled with casts. 100 $\times$. H. and E.

Figs. 2 and 5 show very well the progression of phases of granulomatous transformation of glomeruli.

Diagnosis. Malignant nephrosclerosis with superimposed tuberculous nephritis. Bilateral markedly contracted kidneys with widespread pyelogenous scarring. Marked hypertension and arteriolo-sclerosis. Cerebral hemorrhage with cerebral edema. Marked sclerosis of the basal cerebral vessels. Struma colloidis diffusa. Pseudomucinous cystoma ovaricum. Caseous lymphadenitis involving the para-aortic and paratracheal nodes.

Discussion. The term malignant nephrosclerosis was coined by *Fahr* (5a, c). Synonyms (1-6) in the literature include: malignant hypertension (7), malignant phase of essential hypertension (8), and necrotizing angiitis (9). Necrotizing angiitis is a term commonly used to denote affections of the small arteries with fibrinoid degeneration and necrosis. *Fahr* meant his term to replace the older appellations: genuine contracted kidney (genuine Schrumpf-niere), chronic indurative, or interstitial nephritis (8), and as a

synonym to those of his contemporaries, i.e., *Herxheimer's* arteriolonecrosis (10) and *Paffrath* and *Aschoff's* "red granular atrophy with diffuse spread of the process" (11, 3).

There soon arose differing views on the origin of the two forms of hypertension, benign and malignant, as they were differentiated by *Volhard* and *Fahr*. Pathologists (11) advocated grouping all anatomically identical forms, although they had differing clinical pictures, claiming that they varied only in the extent and distribution of atherosclerosis of small vessels. They grouped pathologically identical cases that were similar clinically, and held a unitarian viewpoint of the genesis of the scleroses. Rejected by most clinicians, to whom a dual origin had a more palatable flavor, there arose the present-day opinion that malignant hypertension is not a disease entity, but a syndrome, in which the hypertension is either primary, or secondary to any of a number of different diseases (12, 12a, 9, 7, 13, 14).

In line with these ideas, *Klinge* (15) put P. nodosa and malignant nephrosclerosis in the ranks of what one now calls "collagen diseases" (*Klemperer*), characterizing them as disease entities designated anatomically by fibrinoid degeneration of connective tissue due to hypersensitivity (similar to that in rheumatic disease).

Similarities between the two have been noted many times (*Kussmaul-Maier*, 1866) (16). *Selye* and *Pentz* experimentally produced P. nodosa in rats by unilateral nephrectomy and overdoses of Desoxycorticosterone acetate (with compensating increased ingestion of NaCl) (17). The result was malignant hypertension. They theorized that abnormal (excessive) adaptive response of the adrenal cortex is an underlying causal mechanism in P. nodosa, malignant hypertension, and rheumatic fever. This theory is not fully proven (9). *Selye* also produced marked hypertension and P. nodosa in rats with large doses of crude anterior pituitary lobe extract. The same factor that converts benign to malignant hypertension may be operative in P. nodosa (18, 19).

Clinicians characterized malignant nephrosclerosis by grouping together clinically identical cases, no matter what the pathogenesis was (20, 7). Such grouping is most commonly used today, and is stated or implied by many authors (12, 9). Thus, it is not a disease *sui generis*, but a complication of several basic diseases, all of which have hypertension as their common denominator. Although

the frequency with which necrotizing angiitis occurs in association with malignant hypertension in man and laboratory animals is too great to be considered coincidental, each condition occurs without the other, no reported series showing an incidence of necrotizing angiitis greater than 85% (9).

The clinical signs of malignant nephrosclerosis are what determines the diagnosis (21), although chronic glomerulonephritides were observed with secondary hypertension which were indistinguishable from cases of primary malignant hypertension (in which case the diagnosis was confirmed at autopsy) (22).

American workers (7, 23) differentiated two types of vascular wall damage in malignant nephrosclerosis: one predominantly degenerative, the other mostly inflammatory. They found necrotizing lesions also occurring in pyelonephritis and glomerulonephritis, with and without the presence of uremia, noting the lesions chiefly in vasa afferentia, sometimes in interlobar and arcuate arteries. Next in order of frequency were the splenic and pancreatic vessels (7, 5c). Renal insufficiency is the terminal phase of the disease, averaging about thirty days (7, 24). The disease is more likely to occur, and be more malignant, the younger the patient, and the higher and more stable the blood pressure (6, 7). Average age of the patients is under fifty years (5, 25, 7). People with benign nephrosclerosis average more than fifty years of age. This point favors a specific causative factor in one not present in the other.

The specific causative factor was mostly suspected to be Lues, lead poisoning, or articular rheumatism in the Continental literature (5, 25).

Other toxic factors were never proven causative: mercury, salvarsan, bismuth and nicotine poisoning, pregnancy, and the menopause (25). Cases are reported of malignant hypertension suddenly superimposed on specific or nonspecific chronic pyelonephritis, unilateral putty kidney (25), chronic glomerulonephritis, adrenal cortical hyperplasia (26), pheochromocytoma (a necrotizing angiitis has been produced experimentally in dogs with large doses of adrenalin, 27), benign arteriosclerosis (28), rheumatic joint involvement (17), administration of Cortisone for P. nodosa (29), basophilic pituitary adenoma (30), and even a post-diphtheritic case (31). There have been cases of P. nodosa combined with a florid malignant nephrosclerosis (25, 32).

Attempts to incriminate these factors (infectious, toxic, mental stress, etc.) have been inconclusive (15, 5d, 26, 33), although experimental work has been very suggestive. The mechanism by which the benign sclerosis is transformed to the malignant is incompletely understood (12). It is known that the high grade dys-oric changes (acute necrosis) in the vessel walls show fibrinoid alteration. In general, the changes are severer, the smaller the vessel caliber. If one allows that the concept of collagen diseases depends on assumption that connective tissue is an organ which is the common seat of a heterogeneous series of maladies (13), then malignant nephrosclerosis is a collagen disease. However, fibrinoid alteration of collagen is not pathognomonic for hypersensitivity in human disease (13).

Fibrinoid arterial necrosis was produced experimentally under conditions precluding hypersensitivity as a pathogenetic factor (34, 35, 36, 37, 38, 27). The hypertensive factor is equally important. Many of the patients, as in our case, were exposed to severe chronic stress, or have an inability to relax, or a driving, restless way of life (25). The severity of the hypertension is related to the intensity of emotional conflict (39, 40, 41).

Kimmelstiel and *Wilson* found close correlation between occurrence of hypertension and renal vascular lesions (42). Presence of necrotizing arteriolitis indicates an unusually severe degree, or prolonged duration of, hypertension (28). *Goldblatt* emphasized that both hypertension and renal excretory functional impairment are necessary for production of arteriolar necrosis (28a). Both benign and malignant sclerosis may depend on hyperemia associated with retardation of renal blood flow (43). From the foregoing material, one concludes that both hypertension and hypersensitivity are probably operative prerequisites to the occurrence of malignant nephrosclerosis.

Clamping the renal artery of rats caused malignant hypertensive lesions in the mesenteries strongly resembling P. nodosa, emphasizing the similarity of these conditions (44).

The disease is characterized by arteriolar involvement of all the organs, especially the kidneys, sometimes with formation of granulomas extremely difficult to differentiate etiologically, as in our case (4, 25, 7, 45). Acute rheumatic miliary involvement can simulate to some degree, tuberculomatous lesions, as well as P. nodosa (46, 47).

Periarteriitis nodosa can represent either extreme of necrosis or granuloma formation histologically. The common feature of malignant sclerosis and P. nodosa is the peculiar arteriolar change, a fibrinoid degeneration, with its basis the precipitation of acid mucopolysaccharides in the connective tissue ground substance (48). It is probably initiated by factors of hypersensitivity, hypertension, and as yet unknown influences: the degree of severity and combination of operating factors giving the appropriate clinical syndrome.

Lesions of malignant sclerosis may be so intense, as to suggest strongly P. nodosa (5d, our case): then no sharp line can be drawn between the two. Occasionally, in rheumatic arteriitis, arterioles of fair size exhibit exudative and necrotizing panarteriitis identical to P. nodosa. Not only does our case resemble strongly a P. nodosa, but the kidneys also contain what appear to be typical tuberculomatous nodules, along with the malignant nephrosclerosis.

This combination is a rare occurrence. Tuberculosis is conspicuous by its rarity in association with hypertension (49). *Holten* cited only fifteen cases of nephritis with tuberculosis in 2,800 cases (33). Tuberculous nephritis of purely toxic origin most certainly does occur (50). Tuberculous foci in and outside the urinary system often produce inflammatory phenomena in kidney parenchyma and interstitium. Characteristically, the urine contains many casts, generous amounts of albumin, few erythrocytes, never many leucocytes, and never any tubercle bacilli. In 2-3% of unilateral renal tuberculosis, a serious nephritis occurs (50).

Investigations of the tubercle bacillus structure showed certain of the bacterial products (phosphatids, phosphatidic acids) have the property of exciting formation of epithelioid cells, from which the Langhans giant cells develop (51, 52). However, it has long been known that the Langhans giant cell is in no way typical for Tuberculosis. They can also be found in Lues, Granuloma inguinale, regional Ileitis, etc. (53).

Rosenthal had a case of panarteriitis, periarteriitis, and terminal hypertension with uremia, in which the patient was tuberculin-negative, as were the lymphnode emulsions on smear, culture, and microscopic section; yet when this material was injected into guinea pigs, sarcoid-like lesions were produced in which nu-

merous acid-fast bacilli were seen. The organisms failed to grow on culture, but the guinea-pigs became positive to tuberculin (54).

The latest articles consider *P. nodosa* and sarcoid-like granulomas as different stages of the same entity; i.e., they are both expressions of a hypersensitivity reaction which is an RES response to tuberculosis antigens. There is subsequent rise in γ globulin antibodies, lymphocyte increase, rise in plasma cells, and granuloma formation. The final picture is of either syndrome or both together (55, 56, 57).

Our case's course was short, but came into the reported range (two months to three years) (7, 12, 18, 24, 25). General symptoms were elicited for only one year. Although she had tuberculous osteomyelitis earlier, no bacilli could be demonstrated by any method. The lymphnodes were typical of Tuberculosis, however, and could have been the source of the toxin producing the nephritis. It must be left open to question, if the ubiquitous renal granulomas are tuberculous, or are secondary sarcoid-like lesions formed as a sequel to a collagen disease.

Summary.

A case of malignant nephrosclerosis combined with sarcoid-like granulomas and toxic tuberculous nephritis is described. The perivascular position of many of these granulomas and the severity of the lesions leads one to think of Periarteriitis nodosa. The various etiologic possibilities of this combined picture are discussed by means of the existing literature. Reference is made to the fact that the malignant nephrosclerosis can be placed in the group of the so-called "collagen diseases".

Zusammenfassung.

In der vorliegenden Arbeit wird ein Fall einer mit sarkoidähnlichen Granulomen und toxisch-tuberkulöser Nephritis kombinierten malignen Nephrosklerose beschrieben. Die perivaskuläre Lage mancher dieser Granulome und die Schwere der Läsionen erinnern stark an eine Periarteriitis nodosa. Anhand der Literatur werden verschiedene Möglichkeiten der Ätiologie des vorliegenden Kombinationsbildes besprochen. Es wird darauf hingewiesen, daß die maligne Nephrosklerose unter die sog. «Kollagenkrankheiten» eingereiht werden kann.

Résumé.

Un cas de néphrosclérose maligne, combinée à une ancienne tuberculose ganglionnaire, a présenté au niveau des reins des images histologiques complexes qui sont décrites dans ce travail. Elles comprennent des lésions ressemblant d'une part à la périartérite noueuse, d'autre part à des granulomes du type sarcoïde. L'auteur commente ces images en se reportant à la littérature : on pourrait expliquer la combinaison rencontrée en faisant intervenir des facteurs immunobiologiques tels que des antigènes tuberculeux, une hypersensibilité combinée à l'hypertension, ou des facteurs inconnus. Il est d'avis que la néphrosclérose maligne peut être groupée parmi les maladies du collagène.

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